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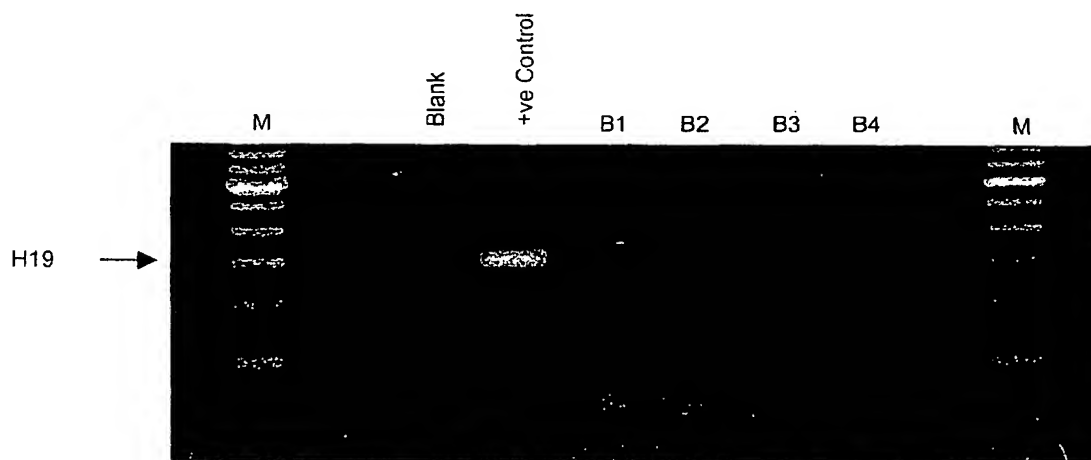
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- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
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- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHOD FOR DETECTION OF MICRO-METASTASIS



(57) Abstract: The present invention concerns a method for the identification of micro-metastasis or residual cancer cells, by identifying the presence of H19 in a sample.

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## INTERNATIONAL SEARCH REPORT

International Application No

US 03/28807

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 7 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, SEQUENCE SEARCH, PAJ, BIOSIS

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TANOS V ET AL: "EXPRESSION OF THE IMPRINTED H19 ONCOFETAL RNA IN EPITHELIAL OVARIANCANCER" EUROPEAN JOURNAL OF OBSTETRICS & GYNECOLOGY AND REPRODUCTIVE BIOLOGY, EXCERPTA MEDICA, AMSTERDAM,, NL, vol. 85, no. 1, July 1999 (1999-07), pages 7-11, XP000992185 ISSN: 0301-2115 *whole document, particularly last paragraph of the discussion*  --- -/--	1-11

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*Z\* document member of the same patent family

Date of the actual completion of the international search

4 March 2004

Date of mailing of the international search report

04/06/2004

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## INTERNATIONAL SEARCH REPORT

International Application No.

US 03/28807

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 955 273 A (ARIEL ILANA ET AL) 21 September 1999 (1999-09-21) cited in the application column 1, line 56 - line 65 column 3, line 55 - line 61 column 4, line 5 - line 37 claims 1,2,8,9,14,15,20,21 ---	1-11
A	SORENSEN BOE SANDAHL ET AL: "Quantification of melanoma cell-specific MART-1 mRNA in peripheral blood by a calibrated competitive reverse transcription-PCR" CLINICAL CHEMISTRY, vol. 46, no. 12, December 2000 (2000-12), pages 1923-1928, XP002269042 ISSN: 0009-9147 the whole document ---	1-11
A	WO 96 29430 A (WAYNE JOHN CANCER INST ;NAT GENETICS INST (US)) 26 September 1996 (1996-09-26) claims 1-20 ---	1-11
A	KIM S J ET AL: "Alterations in promoter usage and expression levels of insulin-like growth factor-II and H19 genes in cervical carcinoma exhibiting biallelic expression of IGF-II" BIOCHIMICA ET BIOPHYSICA ACTA. MOLECULAR BASIS OF DISEASE, AMSTERDAM, NL, vol. 1586, no. 3, 24 April 2002 (2002-04-24), pages 307-315, XP004353587 ISSN: 0925-4439 page 312, column 1, last paragraph -column 2, paragraph 1 page 314, column 2, paragraph 2 ---	1-11
A	OHANA P ET AL: "The expression of the H19 gene and its function in human bladder carcinoma cell lines" FEBS LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 454, no. 1-2, 2 July 1999 (1999-07-02), pages 81-84, XP004259930 ISSN: 0014-5793 *discussion* --- -/--	1-11

# INTERNATIONAL SEARCH REPORT

International Application No

PO 03/28807

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>ARIEL I ET AL: "THE PRODUCT OF THE IMPRINTED H19 GENE IS AN ONCOFETAL RNA" MP. MOLECULAR PATHOLOGY, BMJ PUBLISHING GROUP, LONDON, GB, vol. 50, no. 1, 1997, pages 34-44, XP009012407 ISSN: 1366-8714 cited in the application the whole document</p> <p>-----</p>	1-11

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 03/28807

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☒ Claims Nos.: 12  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
  
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 12

A lack of clarity arises from the wrong numbering of the claims. It appears that 2 claims, one relating to a method and the other one relating to a kit, have been assigned the number 11.

In the following, for purpose of clarity, the claim relating to a kit has been assigned the number 12. It is thus considered that claim 12 relates to a kit for use in any of the methods of claims 1 to 10.

Claim 12 relates to a kit only defined in terms of its function, namely that it can be used in any of the methods of claim 1 to 10. This functional feature is however not sufficient to clearly and unambiguously characterized the claimed kit.

Claim 12 lacks therefore clarity within the meaning of Article 6 PCT. Moreover, the description does not provide any concrete indication as to the reagents contained in the kit, but only a very general statement (see page 13, paragraph '0042!) that does not provide a basis for a meaningful search of claim 12.

Consequently, no search has been carried out for claim 12.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

US 03/28807

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 5955273	A	21-09-1999	IL 108879 A	31-08-2000
			AU 1893095 A	25-09-1995
			DE 69526855 D1	04-07-2002
			DE 69526855 T2	28-11-2002
			EP 0759092 A1	26-02-1997
			WO 9524503 A1	14-09-1995
			ES 2177653 T3	16-12-2002
WO 9629430	A	26-09-1996	AU 5310296 A	08-10-1996
			EP 0871768 A1	21-10-1998
			WO 9629430 A1	26-09-1996
			US 6057105 A	02-05-2000